Cutis/Subcutis Thickness at Insulin Injection Sites and Localization of Simulated Insulin Boluses in Children with Type 1 Diabetes Mellitus: Need for Individualization of Injection Technique?

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The study aimed to describe the variations of cutis/subcutis thickness at insulin injection sites in children with Type 1 diabetes mellitus and to localize the tissue position of a simulated insulin bolus in order to evaluate the need for individualization of injection technique in children. Cutis/subcutis thickness was measured by ultrasound in 47 children (25 girls and 22 boys) without compression (CSCUT) and with compression (CSCT) of the skin at 11 insulin injection sites. Tissue deposition of insulin was measured by ultrasound of a simulated insulin bolus of 200 μl of sterile air injected by the patients using their usual technique and site. On the thigh, 44 % of girls and 95 % of boys had a CSCT of less than 8 mm at one of the measured sites, while 16 % of girls and 50 % of boys had a CSCT of less than 6 mm at one injection site on the thigh and buttock. Significant differences in cutis/subcutis thickness in the same anatomical region were shown. CSCT was up to 35 % less than CSCUT. The air bolus injection was placed inappropriately by 19 % of children (using 8 mm needles). Unawareness of the skin thickness at the injection sites may contribute to inappropriate deposition. We propose that regular ultrasound measurements of subcutis depth at insulin injection sites be taken. This will allow the injection technique to be individualized (vertical or at an angle of 45°). More children would be able to use the simpler vertical technique if 6 mm needles were used where available, or if even shorter (4 mm) needles were produced.

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KEY WORDS **children; cutis/subcutis thickness; insulin injection technique; tissue localization of insulin; ultrasound imaging**

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Introduction

Considerable day-to-day variation in insulin absorption rate has been shown.[1] One of the main factors causing fluctuations in insulin absorption is accidental intramuscular insulin injection.[2,3] Another factor may be differences in cutis/subcutis thickness at insulin injection sites, as an inverse relation between adiposity and the rate of insulin absorption has been described.[4]

Great variations in cutis/subcutis thickness at insulin injection sites have been demonstrated in adults[5] and in one study in children.[6] As many children are lean, and as they use insulin injection needles of the same length as adults (8, 12 or 16 mm), they might be at risk of accidental, inappropriate, intramuscular insulin injection even when injecting at a 45° angle to the skin. Indeed, in a recent study of insulin injection in children, 30.5 % of children using a 12 or 16 mm needle were found to have injected intramuscularly.[7] The children who were injecting intramuscularly were all lean.

This study aimed to detect the tissue position of a simulated insulin bolus (sterile atmospheric air) by ultrasound in children using 8 or 12 mm needles and their chosen injection technique for insulin injection. The study also aimed to describe the variations of the cutis/subcutis thickness in children at various insulin injection sites in order to determine whether there is a need for injection technique to be individualized in children. As the thickness of the cutis/subcutis at the time of the injection may depend on the injection

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technique used, an indication of the maximum and minimum thickness at each site was obtained by measuring the cutis/subcutis with more or less compression of the skin.

Patients and Methods

A total of 47 children (25 girls and 22 boys) with Type 1 (insulin-dependent) diabetes mellitus (Type 1 DM) were examined. Patient characteristics are given in Table 1. Height and weight were measured and body mass index (kg m^{-2}; BMI) calculated. A BMI standard deviation score (BMI SDS) was calculated using the normal reference ranges of Rolland-Cachera.[8] Sexual maturity was assessed using Tanner's criteria.[9,10]

The cutis/subcutis thickness was measured at 11 potential insulin injection sites as shown in Figure 1: three locations on the abdominal wall, six locations on the anterior/lateral thigh, and two locations on the buttocks. Standard real-time ultrasound equipment (Toshiba Tosbee SSH-240) with a 7.5 MHz annular array probe was used.[11] When cutis/subcutis thickness was greater than 40 mm, a 3.5 MHz curved linear probe was used. Two types of measurement were taken. One was performed during a firm and constant pressure on the skin accomplishing maximal compression of the cutis/subcutis (CSCT), which was visually controlled at the ultrasound screen. The other was taken with no pressure (CSCUT). Contact between the probe and the skin was obtained through a layer of aqueous ultrasound contact gel. The same operator performed all measurements.

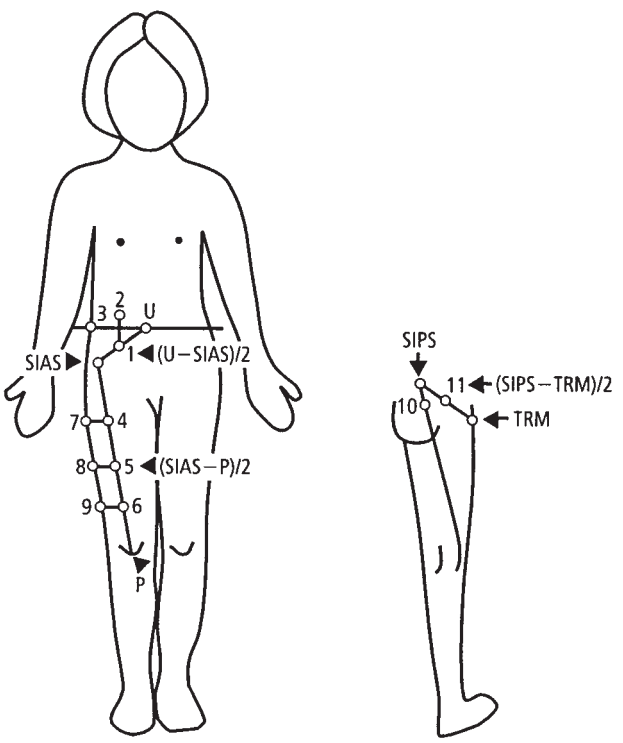

Figure 1. The 11 anatomical measurement sites. U, umbilicus; SIAS, spina iliaca anterior superior; P, patella; SIPS, spina iliaca posterior superior; TRM, trochanter major

To localize the deposition of insulin at these sites, an air bolus of 200 μl was injected by the patient or parent with an insulin pen using their usual technique, needle length (8 or 12 mm), and injection site (thigh, abdomen or buttock). Penfill cartridges containing sterile, atmospheric air to be used in a pen injector device were manufactured by Novo Nordisk for this purpose. The injected air was easily detected by ultrasound in the cutis and subcutis, where it stayed for approximately 30 seconds. If injected into muscle, the air bolus disappeared immediately.

Student's *t*-test was used to evaluate differences between groups, and analyses of variance (ANOVA) were used to evaluate differences in tissue thickness in the same region;[12] p values of less than 0.05 were considered significant.

Results

Table 1 shows the characteristics of the study population. The children used either 8 mm needles (36 children) or 12 mm needles (11 children). The resolution of the ultrasound equipment was 0.2 mm and the total coefficient of variation of five measurements at one site on the thigh was 5 %.

Table 2 shows the mean thickness and range of cutis/subcutis with (CSCT) and without (CSCUT) compression at 11 different insulin injection sites in three different anatomical regions in boys and girls (Figure 1). Except at sites 2, 3, 9 and 11, CSCT was significantly thicker in girls than in boys. The mean thickness was reduced by up to 35 % with compression. The mean reduction by compression was similar in girls and boys except at site 3. The percentage reduction in cutis/subcutis thickness by compression was greatest at the buttock and at the abdomen (27–35 %) and least at the thigh (10–33 %). Great variation in skin thickness between children was found. In particular, at point 2 in girls a range of 2–57 mm was seen. Table 3 shows the number of girls and boys with cutis/subcutis thickness at the 11 measuring sites of less than 8 mm, 6 mm and 4 mm, respectively. On the abdomen, depending on the site,

Table 1. Characteristics of the 47 children

	Girls ($n = 25$) Mean (range)	Boys ($n = 22$) Mean (range)
Age (yr)	11.5 (5.9–17.3)	11.3 (3–18)
Duration of diabetes (yr)	3.6 (0.2–8.5)	4.3 (0.4–11)
BMI SDS Tanner < 2	0.1 (–1.6–1.0)	0.3 (–0.9–2.0)
BMI SDS Tanner ≥ 2	1.2 (–0.3–4.4)	0.9 (–0.6–2.7)
HbA_{1c} Tanner < 2	8.9 (8.3–9.5)	8.6 (6.7–10.5)
HbA_{1c} Tanner ≥ 2	9.4 (7.3–12.6)	10.1 (7.6–13.9)

HbA_{1c}, haemoglobin A_{1c}. BMI SDS, body mass index standard deviation score.

Table 2. Mean and range of cutis/subcutis thickness without (CSCUT) and with compression (CSCT) in boys and girls at 11 measuring sites. XX = the percent reduction in mean cutis/subcutis thickness with compression

Measuring site	Girls ($n = 25$) Mean mm (range)		Boys ($n = 22$) Mean mm (range)		p
CSCUT					
1	15 (3–40)		9 (2–30)		0.04
2	11 (2–57)		7 (2–29)		0.11
3	7 (2–28)		4 (1–23)		0.06
4	13 (3–21)		9 (4–23)		0.02
5	13 (5–24)		10 (5–17)		0.004
6	12 (7–20)		10 (5–17)		0.01
7	18 (3–43)		11 (3–22)		0.004
8	14 (3–26)		10 (4–21)		0.02
9	10 (4–15)		9 (4–14)		0.22
10	26 (7–43)		19 (5–40)		0.02
11	26 (6–49)		17 (3–54)		0.07
CSCT		XX%		XX%	p
1	10 (1–31)	33	6 (1–16)	33	0.04
2	8 (1–31)	27	5 (1–19)	28	0.13
3	5 (1–19)	28	4 (1–14)	0	0.17
4	10 (2–16)	23	6 (3–14)	33	0.001
5	11 (4–19)	15	8 (4–15)	20	0.003
6	10 (5–16)	17	8 (5–11)	20	0.009
7	14 (3–33)	22	9 (3–15)	18	0.002
8	12 (2–22)	14	8 (4–13)	20	0.005
9	9 (3–13)	10	7 (4–11)	22	0.07
10	18 (5–32)	31	13 (7–24)	32	0.01
11	17 (3–32)	35	11 (4–26)	35	0.002

p values for differences between boys and girls.

32–84 % of girls and 55–95 % of boys had a CSCT of less than 8 mm. On the thigh, depending on the site, 16–44 % of girls and 41–95 % of boys had a CSCT of less than 8 mm. On the buttock, 4–12 % of girls and 14–32 % of boys had a CSCT of less than 8 mm. It is remarkable that, depending on the location, only 0–4 % of girls and 0–9 % of boys had a CSCT of less than 4 mm at the thigh and on the buttock.

Figures 2 and 3 show variations in the cutis/subcutis thickness due to sexual maturity in boys and girls. Mean cutis/subcutis thickness was significantly greater in pubertal than in prepubertal girls except at site 6. In boys, however, the difference between prepubertal and pubertal individuals was only significant at sites 1 and 2.

Figure 4 shows the mean CSCT and CSCUT in girls and in boys at six insulin injection sites on the thigh. Significant variations in cutis/subcutis thickness in the same anatomical region were shown with the deepest cutis/subcutis in the upper lateral quadrant in both girls and boys, however the point of the thinnest cutis/subcutis thickness differed in girls and boys with the thinnest cutis/subcutis in the lower lateral quadrant in girls and and the thinnest cutis/subcutis thickness in the upper medial quadrant in boys.

In 38 children (81 %) the air bolus was localized centrally in the subcutis, in six children (13 %) the air bolus was localized on the muscle fasciae, and in three children (6 %) the air bolus was in or just beneath the cutis.

Discussion

The Diabetes Control and Complication Trial (DCCT) has indicated that 'near-normoglycaemia' reduces diabetic complications in adults.[13] Although not investigated, it has been speculated that good glycaemic control in children may reduce the risk of diabetic complications in later life.[14] As insulin absorption shows a day-to-day variation of 25–35 %,[1] a similar variation in blood glucose might be expected. This variation means that reducing mean blood glucose to near-normoglycaemia would risk an increase in episodes of hypoglycaemia,[15] including nocturnal, as the blood glucose levels would now fluctuate around a lower mean point. To keep the mean blood glucose low and avoid hypoglycaemic episodes, the variations in blood glucose must be reduced and the causes of blood glucose variations need further examination. In this study, we examined cutis/subcutis thickness at insulin injection sites and the tissue localization of a simulated insulin bolus in children using 8 or 12 mm needles, in order to help determine how insulin injection techniques might be individualized according to the skin thickness at injection sites.

Large inter-individual variations in cutis/subcutis thickness at insulin injection sites were demonstrated. Cutis/subcutis thickness varied between children: at one location on the thigh, a range of 40 mm, and at one location on the abdomen, a range of 55 mm was observed. Large intra-individual variations in cutis/subcutis thickness at insulin injection sites were also demonstrated. One child, for example, had a skin thickness of 8 mm at one injection site on the abdomen, and a skin thickness of 50 mm at one injection site on the buttock. Great variations in cutis/subcutis thickness at insulin injection sites have also been demonstrated in adult diabetic patients.[5]

At most measuring points, cutis/subcutis thickness was significantly greater in girls than in boys. This was due to an increase in cutis/subcutis thickness in pubertal girls. No such increase was seen in pubertal boys, whose cutis/subcutis mean thickness did not significantly differ from prepubertal boys and girls except at two sites on the abdomen. These findings confirm earlier observations in diabetic and non-diabetic children.[6,16] At all measuring sites except medially on the buttock, several children had a distance from cutis to the muscle fascia less than the length of the shortest needle (8 mm). Compression of the skin (such as often occurs during an injection) radically reduced the thickness of cutis/subcutis, and even more children had a distance from cutis to muscle fascia of less than 8 mm under these circumstances. These children are likely to be at high risk of accidental

Table 3. Number of children with a cutis/subcutis thickness of less than 8 mm, 6 mm and 4 mm respectively without (CSCUT) and with compression (CSCT) at the 11 measuring sites

Measuring site	Girls ($n = 25$)			Boys ($n = 22$)		
	<8 mm	<6 mm	<4 mm	<8 mm	<6 mm	<4 mm
CSCUT						
1	8	7	4	12	10	7
2	15	10	6	16	12	9
3	19	14	5	20	19	12
4	3	3	1	13	7	2
5	4	1	0	6	2	0
6	4	0	0	2	1	0
7	2	1	1	8	3	1
8	4	1	1	7	4	0
9	9	3	0	10	2	0
10	1	0	0	1	1	0
11	1	1	0	3	2	1
CSCT						
1	14	11	6	15	13	9
2	19	16	9	19	13	11
3	21	20	12	21	21	13
4	8	3	1	17	11	3
5	6	3	0	14	5	1
6	5	4	0	10	1	0
7	4	1	0	9	6	2
8	6	1	1	11	5	1
9	11	4	1	18	5	1
10	1	1	0	3	1	0
11	3	2	1	7	4	2

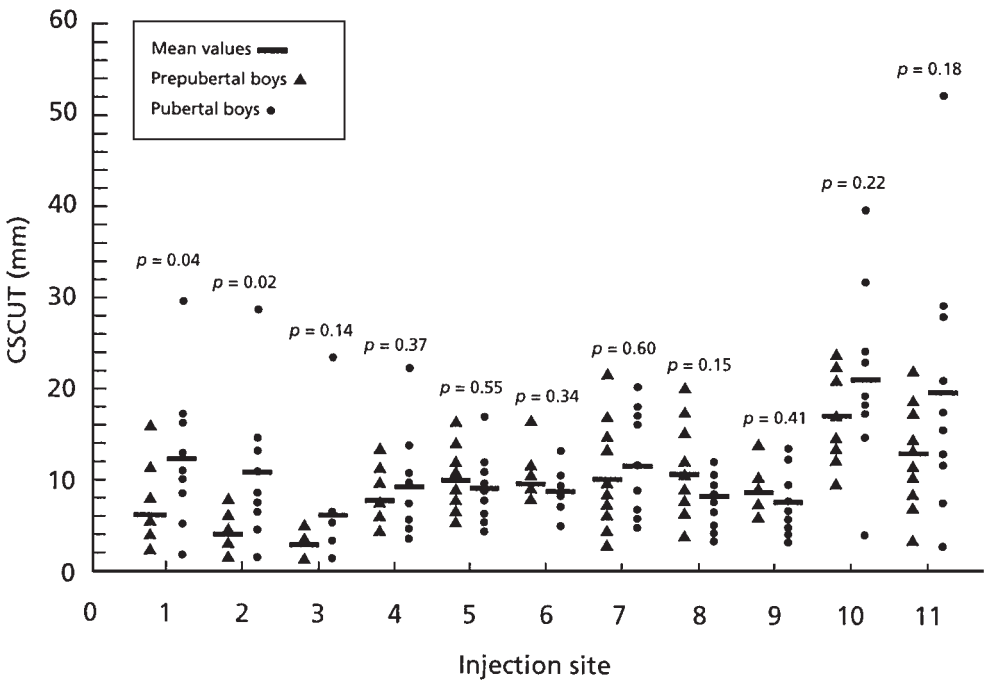

Figure 2. Cutis/subcutis thickness without compression in 12 prepubertal and 10 pubertal boys at 11 insulin injection sites in three anatomical regions. Mean values are marked. *p* values for 2-tailed t-test

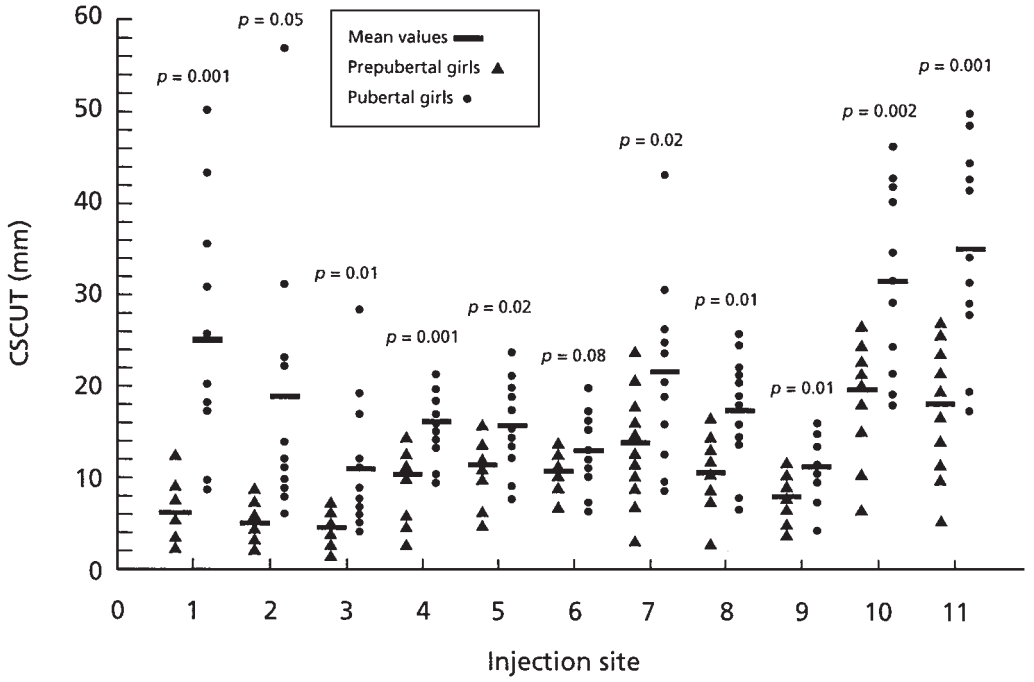

Figure 3. Cutis/subcutis thickness without compression in 13 prepubertal and 12 pubertal girls at 11 insulin injection sites in three anatomical regions. Mean values are marked. *p* values for 2-tailed t-test

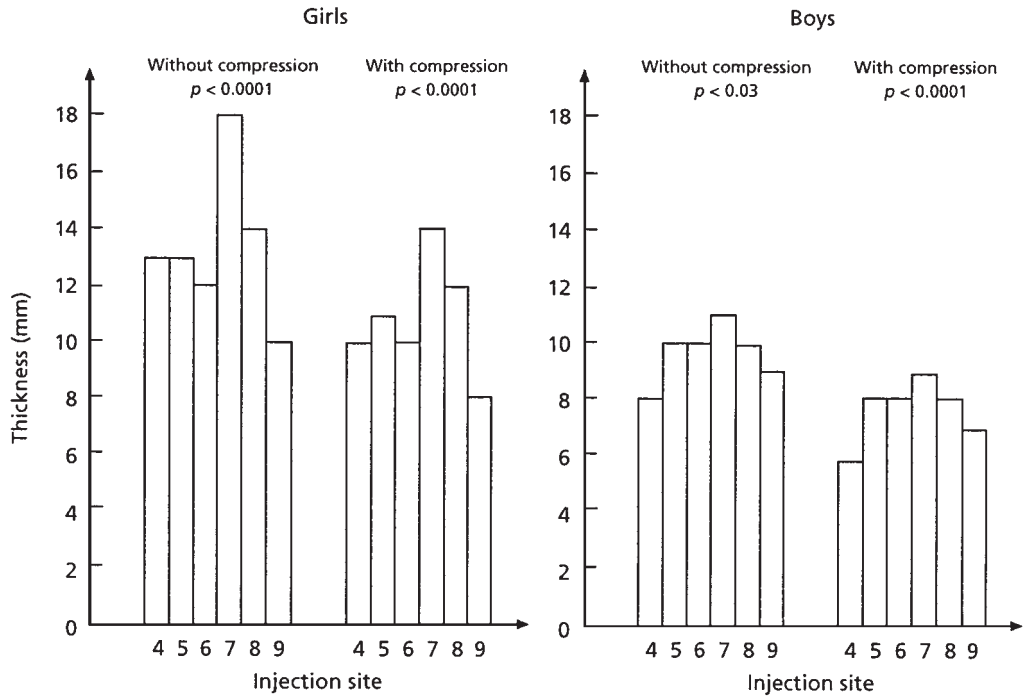

Figure 4. Mean cutis/subcutis thickness with and without compression in girls and boys at six insulin injection sites on the thigh. *p* values for analysis of variance

intramuscular insulin injection. It was observed, however, that few girls but 50 % of boys had a distance from cutis to the muscle fascia of less than 6 mm on the thigh and buttock, but only four children had a CSCT of less than 4 mm at the thigh.

Using their usual technique, 38 patients (81 %) injected the air bolus centrally into the subcutis. Of the remainder, six (13 %) injected into the muscle fascia and three (6 %) injected into the cutis (all of these inappropriate placings were in children using an 8 mm needle to inject at a site on the thigh). Thow *et al.*[17] used an air–water mixture as a simulated insulin bolus and found that 37 % of adults injected into the muscle facia (using 12 mm needles), while the rest injected centrally in the

subcutis. This population was biased, however, as only lean individuals were asked to inject the simulated insulin bolus. In another study, by Polak *et al.*,[7] 30.5 % of children injected intramuscularly. Most of those who injected intramuscularly were male, lean, injected in the arm, injected vertically and all used 12 mm or 16 mm needles. Soluble and neutral protamin Hagedorn insulin are absorbed much more quickly from muscle than from the subcutis of the thigh,[2,3,18] while the absorption rate of soluble insulin in the abdomen is independent of whether the insulin is injected into the subcutis or intramuscularly.[3] Whether the insulin absorption rate is dependent on the location of the insulin depot in the subcutis is currently under debate. One study showed no difference in the absorption rate of soluble insulin whether the insulin was injected at a deep level or superficially into the subcutis.[19] However, all of the individuals in this study were lean. Two other studies found a faster absorption rate for soluble insulin when this was injected deep into the subcutis, but neither of these studies measured the depth of the subcutis.[20,21]

It has been shown that the thicker the subcutaneous fat layer, the smaller the blood flow per unit weight.[22] In accordance with this, an inverse relationship between the thickness of the subcutaneous layer and the insulin absorption rate has been found.[4,23] In our population, large differences in cutis/subcutis thickness in the same anatomical region at the thigh could be shown. As we recommend that insulin injection sites be spread out all over the thigh, this might contribute to the day-to-day variation in the insulin absorption rate.

Compared with Polak's population, who used 12 mm or 16 mm needles, insulin deposition in our study population, who mostly used 8 mm needles, was less likely to be inappropriate. However, 13 % of children injecting too deep and 6 % of children injecting very superficially once or twice a day is a not insignificant number. Although children are taught to inject at 45° into a raised skinfold, during our study we realized that in practice this technique is often modified to a vertical technique (without raising a skinfold). This may be because the vertical injection technique is less painful.[24] This technique may also have the advantage of being more reproducible.[24] Thus, it would be useful if children whose cutis/subcutis thickness was sufficient for them be able to use this technique (perhaps by using shorter needles) could be identified. By regular ultrasound measurements a map could be provided showing skin thickness at injection sites. The child and their parents or carers in co-operation with health care staff would then be able to individualize their injection technique (and needle-length) to position the insulin in the middle of the subcutis. Children with a CSCT at injection sites of more than the shortest needle length might use the vertical technique. The shortest needle length currently available varies between countries; in some it is 8 mm, whereas in others 6 mm needles are available. According to the results of our study, 56 % of girls in our population would be able to use the vertical technique with 8 mm needles when injecting in the thigh. If shorter needles of 6 mm were used, most girls and 50 % of boys could use the vertical technique at both the thigh and buttock.

Conclusions

Great intra- and inter-individual variations in the cutis/subcutis thickness at insulin injection sites in a population of diabetic children were found. Many children had a cutis/subcutis tissue depth of less than the shortest needle available, while others had a cutis/subcutis depth of 3–5 times the shortest injection needle. A total of 19 % of our children injected a simulated insulin bolus inappropriately. Due to the large differences in cutis/subcutis depth at insulin injection sites, we propose that the injection technique in children should be chosen according to the individual's skin thickness at the injection site. The vertical technique – inserting the needle at an angle of 90° without raising a skinfold – should be used where the cutis/subcutis with compression is deeper than the length of the shortest injection needle. This injection technique is easier than injecting at 45°, the insulin is consistently deposited into the subcutis, and it might be less painful if the skin is stretched.[24] The shortest needle currently available in Denmark is 8 mm. If the vertical technique is to be used in lean children, shorter needles (i.e. 6–4 mm) need to be used. Very lean children would probably still have to inject at a 45° into a raised skin-fold. As cutis/subcutis thickness changes through childhood, we suggest regular ultrasound measurements of the cutis/subcutis thickness with and without compression at insulin injection sites for children.

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